Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Guideline on the management of primary resistant and relapsed classical Hodgkin lymphoma.

Bibliographic Source(s)

Collins GP, Parker AN, Pocock C, Kayani I, Sureda A, Illidge T, Ardeshna K, Linch DC, Peggs KS. Guideline on the management of primary resistant and relapsed classical Hodgkin lymphoma. Br J Haematol. 2013 Oct 1; [88 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Definitions for the quality of the evidence (A-C) and strength of recommendation (strong [grade 1], weak [grade 2]) are given at the end of the "Major Recommendations" field.

Prognostic Models

- Repeat biopsy is generally recommended in Hodgkin lymphoma (HL) patients thought to have relapsed, and should be considered in those who have residual fluorodeoxyglucose (FDG)-avid lesions post-therapy (see Figure 1 in the original guideline document) (1C).
- Positron emission tomography/computerized tomography (PET-CT) is the preferred restaging modality after salvage therapy (1B).
- The aim of salvage treatment should be to achieve an FDG-PET-negative remission (1B).

Salvage Chemotherapy

- The choice of a first line salvage regimen in patients eligible for autologous stem cell transplantation (ASCT) should be based on patient factors and familiarity of the treatment centre with the regimen (see Figure 1 in the original guideline document) (2C).
- Regimens containing stem cell toxic agents (such as carmustine and melphalan) should be avoided if possible until stem cells have been successfully collected and cryopreserved if ASCT is planned (1B).
- There is currently no evidence to support intensive sequential induction/consolidation strategies prior to ASCT (1B).
- Consider switching to an alternative non-cross-resistant salvage regimen if there are residual FDG-avid lesions after first line salvage treatment and the intent is to proceed to ASCT (2B).
- In patients not eligible for ASCT, combined modality therapy should be considered, especially in early stage relapse and in patients who have not received prior radiotherapy or who have relapsed outside of the initial radiotherapy field (2B).
- In patients unlikely to tolerate the toxicities associated with more intensive regimens, palliation with either a single agent or with a multi-agent

oral regimen with or without intravenous vinblastine should be considered (2C).
- Early consideration of involvement of palliative care services is recommended, particularly in those not eligible for high dose therapy (1C).

Autologous Stem Cell Transplantation

- ASCT is the standard treatment for patients with relapsed disease who achieve an adequate response to salvage therapy (see Figure 1 in the original guideline document) (1A).
- ASCT is also the standard treatment for patients with primary resistant disease who achieve an adequate response to salvage therapy (1B).
- ASCT is not recommended in those failing to achieve an adequate response (1B).
- An adequate response to salvage therapy is currently defined as a partial response (PR) by conventional CT criteria (2B).
- Choice of conditioning regimen should be based on familiarity of the treatment centre with the regimen (2C).
- Current evidence does not support the use of maintenance cytotoxic therapies post-ASCT (1C).
- Tandem ASCT cannot currently be recommended outside of clinical trials (1C).

Allogeneic Haematopoietic Stem Cell Transplantation (HSCT)

- Allogeneic transplantation using a reduced intensity conditioning regimen is the treatment of choice for younger patients with a suitable donor and chemo-sensitive disease following failure of ASCT (see Figure 1 in the original guideline document) (2B).
- An appropriately human leucocyte antigen (HLA)-matched unrelated donor should be considered when there is no HLA-matched sibling (2B).
- A second autologous transplant is a reasonable clinical option in selected patients with late relapse following ASCT (2C).
- Investigation of the use of allogeneic transplantation earlier in the treatment pathway should be performed in the context of prospective clinical trials, but may be justified in selected patients who have required multiple lines of therapy to achieve a response (2C).

Radiotherapy

- The use of radiotherapy should be given serious consideration in cases of local relapse or relapse at sites where local disease is dominating the clinical picture. The use of involved site techniques is recommended to minimize toxicity to normal tissues (for example, lung fields) if subsequent high dose consolidation therapy is planned (see Figure 1 in the original guideline document) (2B).
- Salvage radiotherapy alone may be considered a reasonable treatment option in selected patients not eligible for ASCT, especially for older patients with relapsed HL who lack B symptoms, have a good performance status, and have limited stage disease at relapse (2B).
- In the rare event of late relapse >5 years after primary therapy occurring at a localized site without B symptoms, treatment with standard-dose chemotherapy and involved field radiation alone may be appropriate (2B).
- Peri-transplant (ASCT) radiotherapy should be considered in patients that have a dominant site of local relapse at an initially involved site (these are usually patients who have had bulky disease with residual abnormalities following salvage chemotherapy and ASCT) (2C).

Definitions:

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context, it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomized clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomized clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series, or just opinion.

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Clinical Algorithm(s)

An algorithm titled "Flow Diagram of Recommended Treatment Pathway for Patients Deemed Eligible for Potential High Dose Consolidation Therapy" is provided in the original guideline document.

Scope

Disease/Condition(s)

Primary resistant and relapsed classical Hodgkin lymphoma

Guideline Category

Evaluation

Management

Treatment

Clinical Specialty

Hematology

Oncology

Radiation Oncology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To aid clinicians in deciding:

- Which patients with primary refractory or relapsed Hodgkin lymphoma should receive salvage therapy with a view to autologous stem cell transplantation (ASCT)
- What response is adequate to allow ASCT and how to determine this
- What is the role of radiotherapy in patient management
- What is the best management of patients unsuitable for autologous transplantation

Target Population

Patients with known or suspected primary resistant or relapsed classical Hodgkin lymphoma

Interventions and Practices Considered

Evaluation

1. Biopsy
2. Positron emission tomography/computerized tomography (PET-CT)

Management/Treatment

1. Salvage chemotherapy
2. Collection and cryopreservation of stem cells
3. Alternative non-cross-resistant salvage regimen
4. Combined modality therapy
5. Palliation (single or multi-agent regimen, with or without intravenous vinblastine)
6. Involvement of palliative care services
7. Autologous stem cell transplantation (ASCT)
8. Allogeneic haematopoietic stem cell transplantation (HSCT):
    - Conditioning regimen for HSCT
    - Donor selection (appropriately human leucocyte antigen [HLA]-matched unrelated donor if no HLA-matched sibling)
9. Radiotherapy:
    - Involved site techniques
    - Salvage radiotherapy
    - Peri-transplant (ASCT) radiotherapy

Major Outcomes Considered

- Association of prognostic factors with patient outcomes
- Efficacy of treatments (e.g., treatment response, freedom from treatment failure, overall survival, local disease control)
- Mortality
- Relapse rates
- Treatment toxicity

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The production of these guidelines involved literature review to Feb 1, 2013 including MEDLINE, PubMed, and the Cochrane reviews database, using 1970 as a start date and the keywords: Hodgkin lymphoma, relapse, refractory, resistant, transplantation, PET, prognosis. In view of the paucity of phase III trials, all series excluding only those that were case reports were reviewed.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context, it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series, or just opinion.

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence (see the "Rating Scheme for the Strength of the Evidence" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The production of these guidelines involved establishment of a working group comprising experts in the field. Development of key recommendations was based on best available evidence.

Due to the paucity of randomized studies the majority of recommendations are based on literature review and a consensus of expert opinion. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) nomenclature was used to assess the strength of recommendations (see the "Rating Scheme for the Strength of the Recommendations" field).

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations

require judicious application to individual patients. Regard as 'suggest'.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Initial review of the manuscript was performed by the British Committee for Standards in Haematology (BCSH) HaemOnc Task Force, and the British Society of Blood and Marrow Transplantation executive committee. Final review was performed by the sounding board of the British Society for Haematology.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate management of primary resistant and relapsed classical Hodgkin lymphoma

Potential Harms

- Toxicity for the majority of chemotherapy regimens in studies prior to autologous stem cell transplantation (ASCT) was mainly haematological, with gastrointestinal toxicity also a common feature of some regimens. Mortality from salvage therapy is low, as expected from the young age of the patients and associated lack of co-morbidities. However, the treatment-related mortality reported for the Dexa-BEAM (dexamethasone, carmustine, etoposide, cytarabine, melphalan) regimen was 5% in the German Hodgkin's Lymphoma study group/European Group for Blood and Marrow Transplantation ASCT phase III trial, although it is hard to know if this reflects an intrinsically greater toxicity for this regimen. Given that no recommendations can be made as to the most efficacious regimen, the decision should be tailored to individual patient needs (such as avoiding cisplatin in renal impairment or avoiding ifosfamide in patients at high risk of ifosfamide-induced encephalopathy) and using an established regimen which is familiar to the treating centre.
- Overall, salvage radiotherapy is safe and well tolerated with mild to moderate acute reversible side effects including fatigue, anorexia, nausea, skin erythema, and dysphagia. The risks of late toxicity should always be balanced against the risks associated with disease progression in this relapsed and refractory setting by experts in radiotherapy of Hodgkin lymphoma, working within the multidisciplinary team. The risk of late toxicity and second cancer risk is dependent on the site, volume, and type of tissue irradiated, as well as age and sex of the patient.

Qualifying Statements

Qualifying Statements

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology, nor the publishers accept any legal responsibility for the content of these guidelines.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Collins GP, Parker AN, Pocock C, Kayani I, Sureda A, Illidge T, Ardeshna K, Linch DC, Peggs KS. Guideline on the management of primary resistant and relapsed classical Hodgkin lymphoma. Br J Haematol. 2013 Oct 1; [88 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Oct

Guideline Developer(s)

British Society for Haematology Guidelines - Professional Association

Source(s) of Funding

British Committee for Standards in Haematology

Guideline Committee

British Committee for Standards in Haematology Writing Group

Composition of Group That Authored the Guideline

Writing Group Members: Graham P. Collins, Department of Haematology, Oxford Cancer and Haematology Centre, Churchill Hospital, Oxford; Anne N. Parker, HPC Transplant Programme, Beatson West of Scotland Cancer Centre, Glasgow; Christopher Pocock, Department of Haematology, East Kent Hospitals NHS Trust, Canterbury; Irfan Kayani, Department of Nuclear Medicine, University College London Hospitals NHS Trust, London; Anna Sureda, Department of Haematology, Addenbrookes Hospital, Cambridge University, Cambridge; Tim Illidge, Institute of Cancer Sciences, University of Manchester, The Christie Hospital, Manchester; Kirit Ardeshna, Department of Haematology, University College London Hospitals NHS Trust, London; David C. Linch, Department of Haematology, University College London Hospitals NHS Trust, London, Department of Haematology, UCL Cancer Institute, University College London, London, UK; Karl S. Peggs, Department of Haematology, University College London Hospitals NHS Trust, London, Department of Haematology, UCL Cancer Institute, University College London, London, UK

Financial Disclosures/Conflicts of Interest

GP Collins, T Illidge, A Sureda, DC Linch, and KS Peggs have acted as consultants for and/or received speaker fees from Takeda. There are no other relevant conflicts of interest to declare.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the British Journal of Haematology Web site .

Print copies: Available from the British Committee for Standards in Haematology; Email: bcsh@b-s-h.org.uk.

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on February 3, 2014. The information was verified by the guideline developer on April 2, 2014.

Copyright Statement

Disclaimer

NGC Disclaimer

The National Guideline Clearinghouseâ„¢ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria.

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.